Access to central veins is critical in the modern era of patient care. Approximately a quarter of central venous access devices, however, become obstructed and must be removed unless they can be reopened (1). The obstruction can be caused by abutment of the catheter tip against the vein wall or by a kink in the tubing, but more than half of the time, the problem is a small blood clot (1). Although all central venous access devices accumulate a thin coat of fibrin, this remains clinically silent unless it extends to block the catheter tip and acts as a one-way valve that permits infusion but not withdrawal (2, 3). If a catheter is not adequately flushed, blood can diffuse into its lumen and form an intraluminal clot that blocks both infusion and withdrawal through the catheter.

In 1980, Hurtubise et al. (4) first reported success in remediying this problem with instillations of thrombolytic agents. They primarily used streptokinase, but soon urokinase became the dominant drug for this purpose until it was temporarily removed from the market in 1999 (5–8). Then alteplase filled the void (8–11). In this issue of Critical Care Medicine, Dr. Svoboda and colleagues (12) report a very large, multiple-center experience using another thrombolytic agent, recombinant urokinase (r-urokinase), to treat obstructed catheters. Their regimen proved to be very effective and safe.

Whether r-urokinase offers any advantage over its predecessors in lysing catheter-obstructing blood clots, however, is not clear. In the only study comparing two thrombolytic agents for restoring catheter patency, alteplase proved to be superior to urokinase (8). Although the urokinase in that trial was not recombinant, it is likely that r-urokinase would have given the same result because its mechanism of action is the same as that of the native enzyme (13).

The study by Dr. Svoboda and colleagues (12) was unusual in two respects. First, one third of the catheters treated were “totally” occluded, which meant that fluid could neither be withdrawn nor infused through them. When infusion is blocked, instilling intraluminal drug becomes problematic. In the large studies establishing the efficacy of alteplase for catheter clearance, catheters were excluded if infusion was difficult (9–11). Simply increasing the infusion pressure is not the answer because of the risk of rupturing the catheter. However, Dr. Svoboda and colleagues (12) were able to infuse enough r-urokinase into all but one catheter to clear the obstruction in 76% of those that were totally obstructed, the same level of success achieved with catheters with only withdrawal occlusion. This was apparently accomplished with three-way stopcocks by using one syringe to create negative intraluminal pressure that was then used to draw r-urokinase into the lumens from a second syringe.

The study by Dr. Svoboda and colleagues (12) also measured the minimal dwell times necessary for r-urokinase to clear the catheters. In previous studies, the success of treatment was often not tested until at least 30 mins after instillation of the drug, although 77% of the central venous access devices in the report by Hurtubise et al. (4) reopened with a mean dwell time of only 22 mins (5, 7–12). In the study by Dr. Svoboda and colleagues (12), 79% of the treated catheters opened with a median dwell time of 15 mins.

Although there were no restrictions on the age of the occlusions in the study by Dr. Svoboda and colleagues (12), there is also no information provided about this variable, which is relevant because as clots age they tend to become resistant to thrombolytic drugs. It seems, however, that most of the obstructions had developed relatively recently. Fifty-six percent of the central venous access devices are described as nontunneled percutaneous types (Table 3), which suggests that they were intended for relatively short-term use and therefore that their obstructions had likely been present for only a few days.

Because r-urokinase is currently not marketed, it is not an option for clinicians faced with treating occluded central venous access devices. However, there is every reason to believe that alteplase, which is currently formulated for this indication, could achieve the same success rates, particularly if it were applied to totally obstructed catheters with the technique used by Dr. Svoboda and colleagues (12). The study by Dr. Svoboda and colleagues (12) also suggests that routinely leaving alteplase to dwell in a catheter for 30–60 mins before testing for patency is probably much longer than necessary in many cases.

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Do not get sick when you are sick: The impact of comorbid conditions*

All clinicians are aware that the presence of one disease may affect the natural history of another disease. Immunocompromised patients are at increased risk for infectious complications, and patients with peripheral vascular occlusive disease are at increased risk for wound infections, to name just two clear examples. The hepatorenal syndrome is another well-described clinical entity where underlying hepatic disease predisposes to the development of renal disorders. There is less awareness of how a critical illness may blunt the host response to an infectious challenge. The article by Dr. Van der Poll (1) in this issue of Critical Care Medicine provides some important insights into these processes. In this article, the authors demonstrate that acute pancreatitis reduces the response to acute pneumonia such that the pneumonia is worse, and the pneumonia also makes the pancreatitis more severe. How does this interaction take place?

Local complications are relatively easy to understand. A patient with poor limb perfusion who develops an infection cannot deliver sufficient oxygen, nutrients, and inflammatory cells to adequately stop the initial focus on infection. From a strictly mechanistic point of view, this is not a challenge to appreciate. Addition-

ally, patients with acute pancreatitis often develop an infection of the necrotic parenchyma (2). The mechanisms here are more complicated and not fully defined. In the area of inflammation, there should be numerous inflammatory cells primed and willing to ingest and kill any invading pathogens. However, it has been documented that neutrophils at sites of inflammation are not as effective in clearing pathogens as those in the systemic circulation (3, 4). Additionally, the systemic neutrophils fail to chemotax efficiently, although this defect occurs later (5). These animal studies have been verified in patients with abdominal abscesses (6). Although there may be a large number of acute inflammatory cells present, they probably do not have the full antimicrobial capacity of their circulating counterparts. Additionally, the necrotic parenchyma provides a protein-rich environment for the growth and proliferation of bacteria. Thus, logical explanations exist for the development of local infectious complications.

What about the development of an infection distant from the site of the initial tissue injury? What hypothesis may be generated to explain how a local disease process sets the stage for subsequent secondary disease? These questions are important clinically, and answers are beginning to emerge. The current communication clearly documents that the presence of acute pancreatitis markedly increases the severity of the pneumonia. This was demonstrated by the increase in the number of bacteria recovered from the lung, as well as increased histology scores, lung weights, and neutrophilic infiltration. The mechanisms of how this occurs may be found in the evidence of increased inflammation in the pancreatitis/pneumonia group relative to pancreatitis group, or the pneumonia group. In other words, the existence of local, comorbid conditions such as pancreatitis increased inflammation and decreased the ability to respond to infectious challenge. This is a very good beginning to understanding the interactions of the immune system, the inflammatory response, and controlled infections.

In the past, investigators have documented that peripheral blood cells obtained from critically ill patients (those with severe sepsis) do not respond as well as those from normal individuals in terms of the ability to generate a cytokine response to an appropriate stimulus (7, 8). Thus, a possible explanation for the present observations is that the circulating cells fail to respond to the pulmonary infection. This may occur through chemokine receptor desensitization. With desensitization, prior exposure to the chemokines impairs the neutrophil’s ability to respond to a second exposure of the chemokine (9). This explanation is unlikely for the present observations since, in the pancreatitis-only group, circulating levels of chemokines were not elevated. Additionally, global immunosuppression is not an adequate explanation since the pancreatitis/pneumonia group had the strongest inflammatory response. Although these data are good beginning, unanswered questions remain.

*See also p. 1997.

Key Words: immunocompromise; infectious complications; acute pancreatitis; acute pneumonia

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Another interesting aspect of the present investigations is the lack of localization of the inflammatory response. Previous publications have documented that pulmonary exposure to an infectious challenge that results in pneumonia produces local levels, but not systemic levels, of inflammatory mediators (10). It was presumed that there would only be evidence of systemic inflammation when there was significant damage to the lung to allow escape of the inflammatory mediators through the injured endothelial cell tight junctions into the circulation. However, the present article shows that in the pneumonia-only group, there was still significant systemic inflammation as demonstrated by the elevated levels of interleukin-6 and the chemokines. The discrepancy between these two publications might lie in the difference between the “two-hit” model in the present article and the single-hit model in the previous report. Thus, the data are clear: Getting sick when you are already sick is not good. This is an area where animal models are underdeveloped. These models have been described as “two-hit” or “two-event” models (11). In the past, mouse models of infectious disease have only been evaluated in healthy, normal, young animals. This fails to recognize the clinical scenario in which infectious complications frequently developed in patients who were neither previously healthy nor particularly young. This is an emerging area of research where evaluation of the inflammatory response to infection is conducted in an animal that has a comorbid or preexisting condition. As this article clearly shows, the inflammatory response is very different when there is a comorbid condition. This will be an exciting area to watch, and the research community should look forward to the results. In the meantime, try to stay healthy before you get sick.

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REFERENCES


Which patient with a do-not-intubate order is a candidate for noninvasive ventilation?*

Noninvasive positive-pressure ventilation (NPPV), first developed as a way to defer endotracheal intubation, has established its role as the primary approach for ventilatory support in many clinical settings. For example, in acute exacerbation of chronic obstructive pulmonary disease, NPPV, in adjunct with medical care before severe acidosis occurs, will reduce endotracheal intubation, treatment failure, and mortality (1). In acute cardiogenic pulmonary edema, asthma, and acute hypoxicem respiratory failure, first-line NPPV also shows promising results (2–4). To avoid complication and discomfort from endotracheal intubation, the use of NPPV has further expanded into more controversial situations, including peri-extubation respiratory failure and do-not-intubate (DNI) orders.

Preliminary studies of NPPV in peri-extubation respiratory failure are encouraging; however, a recent large randomized controlled study demonstrated that NPPV does not reduce reintubation and may increase mortality (5). In this issue of Critical Care Medicine, Dr. Levy and colleagues (6) report on a study using NPPV for patients with DNI orders, some of whom had a do-not-resuscitate (DNR) order. The largest of its kind, this study is the first to provide predictors of hospital survival, using simple bedside characteristics in DNI patients. Nonetheless as a nonrandomized study, it does not test whether NPPV will compare favorably with medical treatment or continuous positive airway pressure. The lack of long-term outcomes (previously reported as poor (7)) and data on comfort, quality

*See also p. 2002

Key Words: noninvasive ventilation; complication; end-of-life; resuscitation; do-not-intubate; do-not-resuscitate

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of life, or patient satisfaction further casts doubt on the merit of this therapy.

Dr. Levy and colleagues found that the overall survival is 43% from their experienced centers, although better results may be expected among patients with congestive heart failure and chronic obstructive pulmonary disease who have a strong cough or are awake. However, for whom are these predictors useful? Should any patient with DNI receive NPPV if favorable predictors are present? In my view, first, it is the patients’ treatment goals—not their diagnoses, not their characteristics—that should govern the use of noninvasive ventilation.

If the goal is to maximize the chance of survival, we must provide the care that serves this goal best: full resuscitation. Partial resuscitation with NPPV—without proceeding to endotracheal intubation when it fails—should be discouraged; this is suboptimal, also violating our ethical obligation of nonmaleficence (8). At best, NPPV alone will give a resuscitative efficacy equal to initial tracheal intubation. For this goal, in fact, a DNI order should be discontinued. Then, NPPV may be used to avoid tracheal intubation and the predictors identified by Dr. Levy and colleagues provided to aid decision. We must know, however, that NPPV is not for the patients with hemodynamic instabilities, inability to protect airway, or lack of co-operation. Lack of experienced staffs is also a relative contraindication. The patients should be informed that most patients with DNI orders who survive one episode of respiratory failure will face another or other life-threatening event soon. Much time could be spent in the hospital—as a so-called revolving-door patient—if the patient survives (7).

On the other hand, if the goal is to avoid discomfort, to survive without trying to maximize the chance of surviving, NPPV should not be offered. In these patients, a DNR order, if not already present, should be recommended because it serves the goal best. For those who believe that NPPV will provide comfort, they should be told that “noninvasive” ventilation is not noninvasive. In fact, it may cause great suffering.

Problems often arise from the positive pressure and its delivering devices, pressing on the face, causing redness, pain, and irritation. Aided by analgesic and sedation, the instrument may continue to press until skin necrosis develops over the nose or mouth (9). The blowing air causes dryness in the nose and throat, and the patients often feel pain in their ear or sinus because of the air pressure. In fact, rupturing of bilateral tympanic membranes can happen (10). The pressure often distends the esophagus and stomach. Esophageal rupture has been reported (11). Gastric distention causing ileus and pain occurs in up to 50% of patients. Unfortunate patients may develop a ballooning of the stomach (Fig. 1) (12). This misery, treated inappropriately, can progress to an abdominal compartment syndrome with cardiovascular collapse (13).

In addition to the direct insults from the machine, collateral damages are substantial. The patient needs close monitoring and frequent arterial blood gas, measured either from an arterial line or by frequent painful punctures. Besides, alarms from devices in the unit, in union with the ones from his or her machine, plus the noises from certain NPPV instruments can reach 100 decibels, interfering with sleep or rest (14). Air leaks around the mask often blow into the patients’ eyes; irritation and tearing are common, and only more air will flow inside to maintain the pressure when it leaks, perpetuating the ordeal. The distress extends to family members, seeing their loved one struggling while fully awake. In addition, how we fix these problems can be troublesome, often making it hard to eat or talk—or finalize affairs. Inadequate cooperation will lead to sedation; gastric distention will result in nasogastric tube placement. In fact, if air leak results from the patient gasping for air during nasal application, we may tell the patient to keep his or her mouth shut (15).

What about those who still prefer to do things in moderation, those who are willing to bear with the NPPV (but not endotracheal intubation) and get a chance of brief survival to finalize affairs? Disappointingly, in the fight for life, there is no benign middle ground. In my opinion, this strategy is not a moderate choice, but a mediocre choice: not producing maximal benefit yet associated with great risk.

Perhaps, patients who wish to finalize their affairs should be advised that at this time in their lives, there are no more burdens to bear, no more affairs to finalize, no more fights to pursue. Let them know that the most important thing is to be at peace with themselves. Also, the myth about morphine should be dispelled: low-dose morphine to relieve

![Figure 1. Ballooning of the stomach. Reproduced with permission (12).](image-url)
breathlessness will not cause excessive drowsiness—it will allow interaction with family members. Oxygen will further relieve the sensation by its direct stimulation of the trigeminal nerve. A private room with loved ones at the bedside will enhance a sense of control—a dignity. With the patients’ unswerving goals and with our therapy tailored toward their goals, we can effectively serve these seriously ill patients. When chances come, we may have the privilege of assisting them through the valley of death, making it a heartwarming, a satisfying experience.

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Eliminating catheter-related bloodstream infections: Fairy tale or new reality?*

I n this issue of Critical Care Medicine, Dr. Berenholtz and colleagues (1) from Johns Hopkins University School of Medicine describe their success using a stepwise, methodical, protocolized approach in decreasing catheter-related bloodstream infection (CRBSI) in the surgical intensive care unit. Results were impressive over the 5-yr study period, during which CRBSI was decreased from 11.3/1000 catheter days in the first quarter to 0/1000 catheter days in the 20th and last quarter. With deserved pride and some fanfare, they footnote no additional CRBSI for 9 months after the study was completed.

Think about that! Zero incidence of CRBSI. CRBSI has been a bane of acute care medicine for half a century. What manner of pixie dust must these clinicians be scattering upon their patients to achieve zero CRBSIs? How was this feat achieved in a venerable, albeit resource-intensive and well-financed, academic medical center? Are we not in Camelot? Is this not a fairy tale? More about this to follow, but first, what has been the recent history of the science of preventing CRBSI?

Early reports (2, 3) describing the extensive use of central venous catheters (CVC) to facilitate the treatment or resuscitation of patients first surfaced after World War II; but the insertion of CVC mainly escalated in the 1960s and 1970s with the evolution of intensive care medicine and the introduction of hyperalimentation (4, 5). More than 5 million CVCs are inserted in the United States each year, with the incidence of infectious complications ranging between 5% and 26% (6). Attributable mortality from CRBSI may be as low as 3%, but there is no disagreement as to the significance of morbidity, increased length of stay, and inflated cost (7). As a consequence, guidelines for the prevention of CRBSI have been issued (8) and the thrust of research in recent years has focused on strategies that enhance infection control methodology and practice. These measures have included standardized educational efforts directed toward CVC insertions (9) and the preference of chlorhexidine antisepsis as a means of reducing CRBSI by nearly 50% compared with povidone-iodine (10). However, the greatest glitz has been reserved for antimicrobially coated CVC.
which are effective at decreasing CRBSI and very costly (11, 12). For example, acquisition cost of a standard-issue triple-lumen catheter at Tufts-New England Medical Center is $22; the cost of an antimicrobially coated triple-lumen catheter is approximately $75. Because the CRBSI rate in our surgical intensive care unit is just 2.6/1000 central catheter days, which is one-half the national benchmark of 5.2/1000 central catheter days for surgical intensive care units (13), we have not been convinced of the cost effectiveness in implementing the high-technology solution of antimicrobially coated catheters. Interestingly, guidelines issued by the Centers for Disease Control and Prevention give a lukewarm recommendation for these catheters, which should be employed only after failure of a comprehensive approach at decreasing CRBSI (8).

The investigators from Johns Hopkins significantly decreased CRBSI using a low-technology, stepwise, comprehensive strategy (1). This strategy included the following: a) standardized education of staff; b) essential grouping of necessary ingredients for a CVC into a single location by use of a vascular line cart; c) discontinuation of no longer necessary CVC by regularly inquiring as to the need through use of a daily goals sheet; d) implementing a catheter-insertion checklist for assurance of sterile technique; and e) empowering the bedside nurse to halt the CVC procedure when a sterile technique was observed to have been violated. This is no pixie dust. These clinicians used neither supernatural magic nor even glamorous high-technology solutions. The result achieved by these clinicians is simply an enchanting mix of hard work, low technology, and most especially the tenacious application of the protocol approach to achieve continuous quality improvement. It may well be that the process of changing care was as important, or even more important, than any of the actual steps used in their multi-faceted approach.

The early notions of quality improvement originated with the American industrial scientists, Walter Shewhart and Edward Deming, in the first half of the 20th century (14). They introduced the concept of “variation reduction.” The use of protocols in intensive care medicine, by comparison, is a belated phenomenon but is rapidly spreading (15, 16). Successful examples in the intensive care arena of an algorithmic, standardized approach to decrease patient morbidity and mortality abound and include weaning from mechanical ventilation (17), use of intensive insulin for strict euglycemia (18), continuous sedation (19), and early resuscitation of patients with severe sepsis (20).

The benefits of the protocol approach are as follows.

1. The application of evidence-based “best practice”
2. The standardization of care
3. Standardized care decreases variability
4. Decreased variation reduces error and complications
5. Fewer complications lead to improved patient outcomes
6. Less error and better patient outcome lead to decreased costs

The gains that result come not from best practice alone but from the constancy of practice that leads to a decrease in errors, improved effectiveness, and the reduction in uncontrolled variables. The construction of protocols requires that one engage intuitive metrics and expedites mission-critical convergence of the available talents and resources in the ICU.

Dr. Berenholtz and colleagues take the eradication of CRBSI to near perfection, shrewdly using a combination of redundancies, prompts, education, assessment, and reassessment. Striving for near perfection is also not new. Industry giants, including Motorola and General Electric, have refined advanced iterations of quality improvement into the concept of Six Sigma. The Six Sigma process uses data and rigorous statistical analysis to identify “defects” in a process, to reduce variability, and to get as close to zero defects as possible. Dr. Berenholtz et al. proclaimed sustained performance improvements, with a CRBSI rate of just 0.54/1000 catheter line days in the ensuing 16 months after the study period. There are precious few documented examples of near perfect care, particularly over an extended period of time, in the annals of critical care medicine. Their example, methods, and degree of achievement are a model for all critical care clinicians.

Clinicians should be forewarned, as prolonged improvements in care are measured more in years than in mere months. The protocol approach is not without flaws. In our own experience with protocols, we have observed a phenomenon that we call “protocol fatigue.”

Protocol fatigue develops when adherence to a protocol is found to dwindle over time, because of new staff, new trainees, erosion of knowledge, and perhaps changes in a given patient population. Recognition of protocol fatigue, best accomplished through periodic measurement with a database such as Project Impact (21), requires protocol revisions to incorporate new scientific advances, renewed energy, and reinvigoration to increase efficiencies. It would be instructive to follow the Johns Hopkins surgical intensive care unit CRBSI incidence over the next 5–10 yrs, as a measure of genuine protocol endurance.

The iterative, protocol approach takes enormous dedication and effort on the part of critical care clinicians. However, in our experience, and as shown in the example herein by the Johns Hopkins investigators, sustained and meaningful improvements in patient care can be achieved with hard work and commitment.

Pixie dust is not necessary.

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Targeting leukocyte trafficking in the treatment of severe trauma*

In this issue of Critical Care Medicine, Dr. Seekamp and colleagues (1) report on an ambitious phase II trial investigating the effect of L-selectin blockade on outcomes after severe trauma. Targeting this adhesion molecule is an attractive choice, for it governs one of the earliest steps in leukocyte trafficking. Under physiologic conditions, neutrophil delivery to a site of inflammation involves a series of leukocyte-endothelial interactions each mediated by a separate set of adhesion molecules. Rolling, the first step of leukocyte trafficking, is mediated by L-selectin. This molecule is constitutively expressed on the surface of most leukocytes. Rolling results in the activation of the leukocyte with up-regulation of surface integrins and shedding of L-selectin. This increase in surface integrins induces a firm stationary bond (adherence) between the leukocyte and endothelial cell. The leukocyte then transmigrates into the interstitial compartment along a chemotaxic gradient toward the site of injury or infection.

In states of systemic inflammation such as severe trauma and sepsis, this orderly procession of leukocyte trafficking is often disturbed. The potent antimicrobial armamentarium possessed by neutrophils can be unleashed on host endothelium. Indeed, neutrophils have been implicated in the pathogenesis of microvascular leakage and end-organ injury leading to multiple organ dysfunction syndrome. Furthermore, severe systemic inflammation interferes with effective leukocyte trafficking (2, 3), potentially increasing the susceptibility to secondary infections. L-selectin appears at the crossroads of both of these potential complications.

L-selectin is shed from the leukocyte surface in severe trauma (4) and septic (2) patients, resulting in increased levels of soluble L-selectin in plasma. Animal studies have demonstrated that high soluble L-selectin levels interfere with leukocyte delivery to inflamed sites (5) and attenuate inflammation-mediated vascular permeability (6). Therefore, elevated soluble L-selectin appears to be a protective mechanism to limit neutrophil-mediated end-organ injury. In support of this theory, several preliminary human studies have demonstrated an association between low L-selectin levels and acute lung injury following trauma or sepsis. Donnelly et al. (7) demonstrated an increased risk of acute respiratory distress syndrome in septic and trauma patients with low soluble L-selectin levels. Previously published in this journal, Rainer et al. (8) documented an elevated rate of acute lung injury in trauma patients with high surface/soluble L-selectin ratios. Low soluble L-selectin levels were also found to be predictive for sepsis mortality in a longitudinal study by Seidelin et al. (9).

Several large animal studies in the mid 1990s attempted to take advantage of the early role that L-selectin plays in leukocyte trafficking and neutrophil-mediated inflammatory injury, with mixed results (10–13). These and other studies laid the groundwork for the current study. Dr. Seekamp and colleagues (1) present the results of a well-organized, multinational, phase II trial designed to assess the safety (primary objective) and clinical efficacy (secondary objective) of an anti-L-selectin antibody in severely traumatized patients. Clinical efficacy was assessed by the quantified Goris multiple organ failure score. A total of 84 patients with severe trauma (Injury Severity Score >25) from 14 institutions in three European countries were randomly allocated placebo or three different single doses of the L-selectin antibody aseluzumab (HuDregg-55). With regard to efficacy of this study drug, no trends or significant difference in Goris multiple organ failure score, mortality rate, length of intensive care unit stay, time on ventilator, or total hospitalization was witnessed. Sample size was calculated solely to be able to detect a 3-point difference in median Goris multiple organ failure score. The study was thus not adequately powered to address these other, clinically significant, outcomes. It would be interesting to know if the authors plan to proceed with a phase III trial given these negative findings, and if so how they will address the sample size issue and which end point will be used. Unfortunately, these issues are left out of the discussion.

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*ISee also p. 2021.

Key Words: L-selectin; trauma; multiple organ dysfunction syndrome; leukocyte recruitment; antibody

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There was a dose-dependent (but not significant) trend for increased infectious complications and leukopenia with aselizumab administration. In the attempt to limit immune-mediated end-organ injury by diminishing the migratory capabilities of neutrophils, it not unexpected to see a reduction in the anti-microbial function of these inflammatory cells. However, as the authors acknowledge, the slight increase in infection (mostly urinary tract infections) with aselizumab is probably not clinically significant. Pulmonary neutrophil sequestration is well documented in states of systemic inflammation and can lead to a diminished circulating pool of leukocytes. However, how L-selectin blockade resulted in increased rates of leukopenia is less clear. Pulmonary neutrophil sequestration is thought to be primarily a mechanical process, independent of adhesion molecules, as the decreased deformability of activated neutrophils results in physical trapping of these cells within the vast pulmonary capillary network. Regardless, the number of patients with leukopenia in each group was too small to definitively determine the clinical consequences of this finding.

The rationale for L-selectin blockade for the prevention of inflammation-mediated end-organ injury is based on strong biological evidence from both animal and preliminary human studies that abounds in the literature. However, it is important for the authors to demonstrate in this present study that the desired biochemical effect on the neutrophil population indeed occurs with aselizumab. The authors do report that the maximum saturation of neutrophil binding sites was high (89%) for all patients receiving aselizumab. However, this finding may not be due solely to L-selectin blockade but also to increased L-selectin shedding in these patients. Neutrophil activation and L-selectin shedding due to surface L-selectin cross-linking with L-selectin antibodies such as that used in this present trial (HuDregg 55) are well described (14). Therefore, the authors’ findings may be due to a decrease in overall surface L-selectin rather than L-selectin blockade. In turn, this could result in increased soluble L-selectin levels in patients receiving aselizumab. Unfortunately, the authors did not assess the level of soluble L-selectin at any time point in this study. Although this may not alter the safety and efficacy outcomes, it may facilitate the identification of addressable problems with this negative study. Furthermore, an assessment of the biological effect, namely reduced neutrophil delivery, would have greatly strengthened the study and provided valuable information with which to proceed to a phase III trial. Determination of neutrophil content of bronchoalveolar lavage fluid could have readily provided this data.

Overall, the authors are to commended for undertaking an ambitious trial in trauma patients targeting leukocyte trafficking ability. Although it is essentially a negative trial, much clinical data can be derived from this study for the planning of a phase III trial. However, in proceeding toward future anti-IL-18 or other adhesion molecule trials, it is of vital importance to consider the dual nature of the activated neutrophil in states of systemic inflammation. Limiting the deleterious systemic effects of activated leukocytes is an appealing target for therapy. However, decreased neutrophil recruitment to remote sites may also negatively affect host susceptibility to infectious pathogens. Therefore, improved outcome from severe trauma patients hinges on manipulating a fine balance between diminishing leukocyte-mediated end-organ injury yet maintaining effective leukocyte-dependent host defense.

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Crit Care Med 2004 Vol. 32, No. 10
Albumin versus crystalloid solutions for the critically ill and injured*

Albumin in solution, a heart-shaped molecule, has multiple functions as building blocks. It serves as a carrier for fatty acids and other water-insoluble metabolites, as a binding site for hormones and drugs to facilitate transport of vital substrates, and as the primary colloid of plasma by which it controls the balance between colloid osmotic and hydrostatic pressure in capillary exchange vessels. A critical deficit in the plasma concentrations of albumin, as in liver disease or congenital analbuminemia, is associated with clinical edema. Almost 80% of Canadian physicians who were polled in the province of Ontario recently prescribed colloids for the management of critically ill patients (1). Nevertheless, a vigorous debate continues regarding the therapeutic benefit of infused albumin solutions or, for that matter, colloidal fluids more generally in contrast to crystalloid and especially electrolyte solutions for fluid management of critically ill and injured patients.

Systematic reviews of outcomes based on meta-analyses of randomized, controlled trials have produced directly conflicting results with respect to mortality. In this issue of Critical Care Medicine, Dr. Vincent and his collaborators (2) again sought to establish the clinical benefits of albumin solutions but sought a criterion other than mortality, namely, complication rates. From an initial review of 484 potential reports, the authors relied on 71 randomized trials for their meta-analysis, including almost 3,800 patients. They concluded from this analysis of an impressively large number of patients who were resuscitated with albumin that the combination of albumin and crystalloid fluids reduced the incidence of complications compared with non-albumin-containing parenteral fluids.

In 1998, it was the Cochrane Injuries Group Albumin Reviewers (3) who published a systematic review to establish whether the administration of human albumin or plasma protein fraction affected mortality compared with crystalloid solutions in critically ill patients. Their findings were based on 30 randomized trials, including 1,419 patients, fewer than one-half the number included in the study by Vincent and colleagues. The Cochrane group reported that the relative risk of death for patients defined as hypovolemic was substantially greater with albumin than with crystalloid, a relative risk of 1.46. The risk alarmed the profession because it projected one extra death for every 17 critically ill patients treated with albumin or plasma protein fraction. The mortality was even greater in patients with burns with a relative risk that was approximately two and one-half times greater. The results were widely reported to the public in the electronic and print media, and the use of albumin declined steeply (4). Meta-analyses do have the potential of resulting in major changes in clinical practices!

In 1999, another meta-analysis by Choi et al. (5), which included 17 studies on 814 patients, failed to support the Cochrane study. These investigators found no difference in the total group when colloid and crystalloid solutions were compared, neither with respect to mortality nor with the incidence of pulmonary edema. Yet, this study also provided evidence that there may be a mortality benefit of crystalloid solutions for patients after traumatic injuries.

The most recent meta-analysis, which preceded the meta-analysis of Vincent et al., was by Wilkes et al. in 2001 (6). It included 55 trials on 3,500 patients. This systematic review also focused on mortality. Once again, there was no overall difference.

The preponderance of clinical studies understandably enrolled a diversity of critically ill and injured patients without specific reference to the underlying disease states, the severity of illness or injury, the magnitude of concurrent interventions including surgical operations, blood transfusions, and concurrent drugs and fluids, and the length of hospitalization. The data were focused on whether colloid or crystalloid fluid was infused but not for the amounts administered. Importantly, subgroup analyses were typically post hoc, and, therefore, suspect (7). Crossovers and potential publication bias in the review of negative data further complicated these efforts (8). It is apparent that a huge number of uncontrolled variables constrained the interpretation of outcomes and ultimately for each of the meta-analyses.

In the absence of concurrence on outcomes based on mortality, we compliment Dr. Vincent and his associates for defining an alternative measurement of value, namely, complication or adverse event rates. They found that the frequency of complications was significantly lower in albumin-treated patients. Although this new endpoint of efficacy or effectiveness is quite appropriate, it also is suspect. Even their conscientious effort to maintain objectivity did not allow for secure categorization. The study was by definition retrospective and nonquantitative. It sought to classify complications in patients with diverse disease states, in diverse organs and systems, and at diverse stages in the clinical course. Iatrogenic complications independent of the underlying disease states were likely to be of moment. It is these variables that are again likely to explain the inconsistencies of outcomes, whether based on morbidity or on mortality. These considerations, notwithstanding, however, the majority of studies, again project a trend favoring...

*See also p. 2029.

Key Words: albumin; colloid fluid; crystalloid fluid; meta-analyses; fluid resuscitation; trauma; hypovolemia

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crystalloid over albumin for patients with traumatic injuries who are likely to be more uniformly categorized.

These are the limitations of currently published randomized, controlled trials that constitute the databases of meta-analyses. Yet, meta-analyses may be the only guide that clinicians have in the absence of more conventional and well-controlled large scale multiple-centered studies in which criteria for entry of patients are narrowly defined and complied with. The most recently published multiple-centered study by the SAFE Study Investigators (9) more closely fulfills this goal. It was sponsored by the Australian and New Zealand Intensive Care Society Clinical Trials Group and was immunized from commercial bias. The SAFE Study included almost 7,000 critically ill patients. In the opinion of the undersigned, it trumps all previous studies that address one of the most fundamental and contentious issues in critical care medicine. The protocol of the study was disarmingly simple in design, and the study was remarkably well organized and controlled. A password protected, internet-based system secured unbiased randomization and assignment. Prompt implementation was facilitated by overcoming earlier ethical constraints, in that the investigators did not have to delay treatment for informed consent by adopting the delayed option consent. Innovative packaging precluded clinicians from distinguishing between albumin and crystalloid fluids before, during, and after fluid administration. The reported outcomes were persuasive (9). Mortality did not differ significantly between patients assigned to either the albumin or the crystalloid (saline) group. Secondary endpoints, in part, comparable with the complications analyzed by Dr. Vincent and colleagues, including the duration of mechanical ventilation, the incidence of renal failure, and the length of intensive care unit and hospital stay, did not differ. Again, there was a trend suggesting that albumin had adverse effects when administered to patients after traumatic injuries.

What are we to conclude? First, for the majority of critically ill and injured patients, there is no secure evidence of benefit of colloid, including albumin over crystalloid solutions. Yet, as suggested by the analysis of Vincent and colleagues, it is almost certain that selective pathophysiological states may be benefited by one fluid over another. In the instance of traumatic injuries and perhaps elective surgical operations, the trend favoring crystalloids, although incomplete, is consistent over the horizon of major meta-analyses and the independent multiple-centered SAFE trial. This contrasts with patients with major medical complications, such as hepatorenal failure, severe hypoproteinemia with edema, or major infectious complications, for whom colloid, including albumin, may ultimately prove to be more beneficial.

It is, therefore, appropriate, in the opinion of the undersigned, to encourage additional and well-designed randomized multiple-centered studies but on patients who are enrolled with more narrowly defined disease states and specific organ dysfunction to confirm or reject special indications for or against albumin (7). Until then, we interpret the current evidence as inconclusive. Excepting traumatic injuries, we would hesitate to recommend one fluid over another under the very large umbrella of “critically ill” patients. This is a conclusion to which we have been led by the evidence herein reviewed, admittedly revising our yesteryear allegiance to colloid fluids, including albumin and hydroxyethyl starches (10, 11).

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REFERENCES

The deceptive complexity of “simple” proning*

Frequently reorienting and readjusting body position are defining mammalian characteristics. During health, matching of ventilation to perfusion in the face of these positional variations is accomplished by intricate adaptive mechanisms that include the “passive” influences of structure and gravity and the more “active” regulators of ventilation and perfusion (1). In addition to gravity, distortions of the lung required by obligatory shape matching of lung to chest cage alter the distribution of local pleural pressures. The resulting modifications of transpulmonary pressures influence local alveolar stretch, ventilation gradient, and vascular resistance. Acting independently, gravity also affects blood flow—at least in part—via the classic (if imperfect) “zoning” concept first popularized >4 decades ago (2–4). Active regulators of ventilation and perfusion include autonomic controls, hypoxic vasoconstriction, and variations in local PCO2 and pH.

Although these mechanisms of positional ventilation-to-perfusion adaptation apply to most warm-blooded animals, species differ with respect to tolerance to full inversion of their natural positions. With the exception of certain arboreal animals (e.g., the sloth, opossum, and resting bat) who orient “belly up” in high places to protect themselves from predators, the supine position is never maintained for long. The default body position is prone, even for our closest primate relatives (e.g., chimpanzee, orangutan, and mountain gorilla). Apart from allowing the potential for immediate mobility for feeding, fight, or flight, proning helps to protect the vulnerable vascular structures from predatory attack. In fact, certain species used in experimentation, such as the sheep, are highly intolerant of protracted supine positioning. (Sheep ranchers understand this well—“sheep tipping” to reestablish a prone orientation is a vital daily activity to prevent loss of livestock unable to “right” themselves on their own.) In the large animal laboratory, investigators soon learn that sheep must be carefully monitored and supported when studied supine.

Perhaps it is not surprising then, that in an impressive study of anesthetized healthy sheep appearing in this issue of Critical Care Medicine by Dr. Johansson and colleagues (5), the authors report major differences in the distributions of ventilation observed in the supine and prone orientations—a point reflected in the prior work of others. Of more novel interest is their finding that 10 cm H2O positive end-expiratory pressure (PEEP) improved the homogeneity of ventilation in prone sheep but merely displaced the heterogeneous distribution of ventilation to a more dependent plane in supine animals. Even within a given isogravitational tissue plane, the response to PEEP differed with position, suggesting that factors other than those intrinsic to the structure of the parenchyma were at work. These results, which indicate unexpectedly heterogeneous ventilatory responses to PEEP with position change, are qualitatively similar to those reported previously regarding perfusion (6). Although the authors exercised admirable restraint in reframing from speculation as to the possible explanations for these unexplained positional differences, the influence of position on the heart, mediastinal structures, and lymphatic drainage patterns comes quickly to mind.

Together with earlier data obtained from normal and lung-injured humans (7, 8), the data of the current study strongly suggest that proning reduces the gradient of regional transpulmonary pressures in healthy and in acutely injured lungs. This is good news when there is a need to use relatively high airway pressures to maintain adequate gas exchange, as uniformity of transpulmonary pressures allows a more predictable effect of a single airway pressure profile applied to the airway opening. More uniform mechanical properties presumably lessen the potential for raised airway pressure to cause regional overdistention, adversely redirect blood flow, and predispose to dependent ventilator-induced lung injury.

It is tempting to extrapolate from such experimental observations to suggest that PEEP used in the clinical setting might help maintain recruitment with less potential for overdistention and deadspace creation in the prone position; however, the implications of these laboratory data for the setting of acute lung injury occurring in humans are hardly straightforward. Somewhat in contrast to the data reported by Dr. Johansson and colleagues (5) from healthy lungs, computed tomographic studies in patients with acute lung injury indicate that PEEP applied in the supine position tends to beneficially alter the aeration and ventilation patterns, improving the aeration (and presumed ventilation) of dependent lung regions (9). Among other important variables, the magnitude of such effects would be expected to depend strongly on the nature and severity of injury, recruitable ability of the injured lung tissue, levels of PEEP and plateau pressure, and chest wall configuration.

One nonbiological feature of position change that has received little attention in laboratory-based and clinical scientific literature could also prove influential in modulating the PEEP response. The firmness and form of the supporting surface against which the subject rests influence regional chest wall compliance, modify the shape of the thoracic cavity (10), and potentially may influence the translocation of blood between the abdominal and chest cage compartments (11). As in most reports, the study by Dr. Johansson and colleagues (5) did not characterize the table contour (e.g., flat vs. V-shaped), but I think it safe to assume that the surface was rigid, or nearly so—quite unlike the air-cushioned mattresses that typify the modern intensive care unit. One might also wonder what impact the animal’s states of hydration, anesthesia, and breathing pattern might have made on the study outcome. The technically demanding methods used to track regional ventilation possibly could be influ-

*See also p. 2039.

Key Words: ventilation/perfusion; positioning; alveolar stretch; ventilation gradient; vascular resistance

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enced by the selection of a different tidal volume range or inspiratory flow rate and delivery profile as well. In short, we must respect the potential for interplay among the multiple variables that might have led to the conclusions of this excellent study before attempting to generalize them.

Whatever the limitations of such data might have for clinical applications, they underscore the power (and complexity) of a deceptively simple positional change on physiologic variables of vital concern to the practitioner. This type of investigation, which used sophisticated technologies to reexamine a common and “well-understood” bedside intervention, must be encouraged if critical care therapeutics are to advance.

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REFERENCES


Through a glass darkly: The brave new world of in silico modeling*

Silicon, the 14th element of the periodic table, is, after oxygen, the second most common element on the planet, and the seventh most abundant element in the universe. Its compounds take the form of sand, rock, and glass; it is also the raw material used to etch the microchips that have made the computer revolution possible. And, in this incarnation, it has lent its name to a new mode of scientific inquiry. Where in vivo studies are performed in living organisms and in vitro studies are undertaken using isolated cells or biological molecules, in silico studies use the enormous computational powers of the computer to mine large databases looking for patterns or to integrate large amounts of data to model complex phenomena. The uses of these models are diverse, from weather or earthquake forecasting to modeling potential terrorist attacks to asserting the plausibility of the Biblical flood. Inevitably, too, they are finding a role in biomedical research.

In this issue of Critical Care Medicine, Dr. Gary An introduces an innovative in silico approach to the study of critically ill patients (1). He hypothesizes that an approach known as “agent-based modeling” can replicate the interactions between elements of the innate immune system and so predict the consequences of manipulating these in patients with sepsis. It is a bold task. That his initial forays into this uncharted territory are not completely convincing reflects the magnitude of the challenge and the novelty of the approach more than the aggregate consequences of their interactions. However, it is equally plausible that the performance of the model is critically dependent on the specific assumptions of its inputs, and if this is the case, then the credibility of the approach hinges on the reliability of the data it uses.

A valid model of in vivo biology, whether a conceptual construct or a computer algorithm, presupposes an accurate representation of three separate influences. First, the model must account for most or all of the relevant inputs, considering their identity, their isolated activity, and the magnitude of their effect in response to a stimulus. Second, it must reflect knowledge of the interactions of each of these components with other potential targets that can modify the outcome. These may be complex. The clinical biology of sepsis, for example, encompasses not only the direct effects of the microorganism on the host, but also the indirect effects of the systemic activation of an inflammatory response, the

*See also p. 2050.

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anti-inflammatory or procoagulant response to this response, and the further response of the host to injury resulting from these processes (3). Finally the model must account for the impact of other external stimuli (in the critical care context, the effects of clinical intervention). These, too, are complex and variable, shaped by culture, knowledge, experience, prejudice, fatigue, and a host of other human attributes. Moreover, clinical intervention is not stable over time, but rather changes in response to the adoption of new knowledge.

Dr. An has included a number of cells and soluble mediators in his computer model; however, the activity of each of these is not independent of the others, and many potentially important influences are excluded. For example, acute endotoxin exposure triggers the expression of >300 genes in neutrophils (4) or endothelial cells (5), whereas sustained exposure can evoke a state of tolerance (6). Moreover, most of the genes incorporated into his model are those expressed early following insult, rather than later, and potentially more clinically relevant mediators such as HMGB-1 (7). His model leaves out the potential influence of the infecting microorganism (8), but at the same time, proceeds from the optimistic assumption that administration of antibiotics will convert the outcome from a basal lethality of 100% to 38%, and even more remarkably, from 86% to 37% in patients without infection. The magnitude of benefit documented in clinical trials is much smaller, perhaps of the order of 10% (9). Conversely, the impact, both positive and negative, of the totality of other intensive care unit interventions is not included.

How does one quantify the influence of any single component of a model so that its manipulation in silico will faithfully produce the systemic alterations that would occur if they happened in vivo? Dr. An draws on narrative reviews to characterize the biological roles of the cells and mediators he has incorporated into his model. The approach emphasizes prevailing generic concepts about the activity of a given cell or molecule, over the specific and often contradictory biological detail that characterizes original scientific investigation. Whether the consequence of this approach is a balanced picture of in vivo biology, or simply a tautology (the model predicts a conclusion because it incorporates the individual assumptions that lead to that conclusion) is difficult to ascertain. Clearly, the reliability of an in silico model hinges on the methodology used to provide data for the computer algorithms, whether those data are a compilation of interacting biological processes as presented here or, for example, the sequence of base pairs that comprises the human genome. How this is best accomplished and validated is unknown and an important area for future work.

Dr. An’s model addresses the dynamics of the innate immune response, postulating that derangements in innate immunity underlie the systemic inflammatory response syndrome (SIRS), and its pathologic consequences, the multiple organ dysfunction syndrome. As an abstraction, this concept is well accepted (10). The challenge, however, for both Dr. An and the clinical researcher lies in translating an abstract concept into a set of clinical criteria that define a disease. SIRS is not a disease but a concept that has been operationalized through a series of nonspecific physiologic criteria that have no clear pathologic correlate (11, 12). Not all patients with tachycardia and hypothermia are endotoxic, and not all patients with elevated circulating levels of tumor necrosis factor manifest leukocytosis or tachypnea. Treatments that can ablate SIRS are readily available (β blockers for tachycardia, central cooling for hyperthermia, cyclophosphamide for neutrophilia, and muscle relaxants for tachypnea), but obviously, none of these will reverse the disorder of innate immunity that is believed to kill patients with sepsis. And, while therapies that target tumor necrosis factor have had, at best, only very limited utility when administered to patients with SIRS (13), they have been much more effective when given to patients with inflammatory bowel disease (14) or rheumatoid arthritis (15). Is this discrepancy a function of biology or taxonomy? Has Dr. An succeeded in modeling the biology of sepsis, or simply duplicated the imprecision of classification that results in heterogeneity in clinical trials?

Proof in science lies in the ability to predict an outcome; consistency in predictive capacity is tantamount to scientific truth. The fact that eclipses of the moon or conjunctions of the planets can be predicted centuries in advance is compelling proof of the Copernican model of the solar system, even though scientists will never be able to observe from afar the movements of the planets around the sun. The role of insulin deficiency in diabetes is established by the certainty that administration of insulin will reproducibly lower blood glucose levels and delay disease progression. In statistical terms, proof is supported by rejecting the null hypothesis that there is no effect. Dr. An’s models are consistent with a body of clinical trials data in that they fail to demonstrate an effect resulting from manipulation of the innate immune response. But as the science of in silico modeling evolves, it will be important to validate the concept by showing that it can predict an effect and not simply support the null hypothesis.

Innovation is important but risky, and the innovator leaves himself or herself particularly vulnerable to the skepticism of those whose ideas are entrenched. Dr. An has opened an important new window on the study of an immensely complex process. We look forward to its evolution.

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This issue of Critical Care Medicine contains reports on two projects that model inflammation and sepsis. One project, conducted by Gary An (1), explores the aggregate behavior of a model of the microvasculature at the endothelial-blood interface, in which agents representing constituent cells and molecules interact according to a simple set of rules inferred from recent literature. The other project, led by Gilles Clermont (2), employs a set of differential equations to suggest not only why some recent clinical trials of anti-inflammatory therapies failed, but also how in silico modeling could inform and refine design of future immunomodulator trials.

What is a mathematical model? The usual definition—a symbolic description of the essential interrelations among all elements of a system—underplays both the principles of modeling, as well as its importance to critical care medicine. Mathematical models are to physiology what medical illustrations are to anatomy. No one would confuse a drawing of the heart with the heart itself, yet such medical drawings facilitate our understanding of the organization of the heart precisely because the illustrator abstracts and interrelates only key features of the anatomy. A medical illustration is thus a pen-and-ink model of the actual anatomy; importantly, it is a static model. Although the drawing may include arrows to suggest flow and dotted lines to suggest motion, it makes no prediction about functional change. Drawings and other static models can be verified only by inspection.

Mathematical models of physiology are dynamic. Their purpose is predictive description—to suggest what happens over time. As such, mathematical models are testable hypotheses. When a mathematical model predicts measurable behavior that emulates the physiology under study, one can reasonably infer that the mathematical model has, in fact, captured all of the essential interrelations. Conversely, when model and experiment disagree, something is wrong or missing from the model.

Mathematical models should not be confused with blueprints, either. Blueprints specify systems that have predictable behaviors. In both reports, An and Clermont et al. describe unexpected, even counterintuitive, “emergent” behaviors that arise from the model specifications.

Dr. An populates his agent-based modeling framework with a collection of cells (endothelial cells, neutrophils, receptors (L-selectin, CD 11/18), and mediators (tumor necrosis factor, interleukin-1)). The endothelial cells are fixed in space, the other cells can move around or stick, depending on local receptor and mediator states. Importantly, there are random components to the model—cells can move in one direction, or another. Interactions happen most of the time, but not all the time. Despite this stochasticity specified by the model—in fact, because of it—Dr. An’s agent-based model produces behaviors that correspond to the “two-hit” description of immune-suppressed multiple organ dysfunction syndrome. The “two-hit” phenomenon is not programmed into the model but rather arises as emergent behavior from the specifications that govern interaction among the agents.

Dr. Clermont and his colleagues employ deterministic differential equations in their model but use a cohort of virtual patients who differ slightly (and plausibly) from one another with respect to bacterial load, bacterial virulence, timing of intervention, and heritable robustness in the face of stress. Once those (virtual) patient-specific conditions are established as parameters in the set of differential equations, the outcome for each patient is predicted precisely. Just slight variation in initial conditions and in the timing of interventions—variation that mirrors the clinical reality (and contrasts the reproducibility of inbred laboratory animals subjected to experimental sepsis)—is sufficient to produce model behaviors in which anti-mediator “treatments” produce excess “mortality” in silico. This excess mortality in silico was neither planned nor programmed into the model any more than excess mortality was anticipated or programmed into the clinical trials of inflammatory modulator therapy. Yet, both in silico and in the intensive care unit, excess mortality is a surprising and unwelcome behavior.

No one in the modeling community would suggest that mathematical modeling is a substitute either for animal experimentation or for clinical trials. However, these two reports suggest that modeling of critical illness and intervention serves at least two purposes. First, any model that predicts behaviors closely corresponding to experimental and/or clinical observation reassure us that the model has, in fact, captured all of the relevant components and their interactions. Second, and perhaps most important, discordance between the model’s be-

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*See also p. 2050.

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In vivo, in vitro, in silico...*
Do not suction above the cuff*

Salivary secretions are common in the oropharyngeal cavity of the critically ill who require mechanical ventilation in the intensive care unit (ICU). The upper airway secretions also accumulate above the endotracheal tube cuff, allowing for leakage of these secretions into the lower airways. These respiratory secretions are contaminated with “normal” (e.g., *Streptococcus pneumoniae*) and “abnormal” (e.g., *Pseudomonas aeruginosa*) potential pathogens. The accumulation of contaminated secretions above the cuff is thought to increase the risk of microbial migration into the lower airways and subsequent endogenous pneumonia associated with ventilation. Removal of pooled secretions through suctioning of the subglottic region, termed subglottic suctioning, is thought to reduce pneumonia. This requires the use of a specially designed endotracheal tube with a separate dorsal lumen that opens into the subglottic region. Subglottic suctioning was first described in France in 1992, and since that time, it has been evaluated in four randomized, controlled trials (RCTs) (1–4). The impact of subglottic suctioning on pneumonia and mortality was compared with that of a conventional endotracheal tube in 828 patients over the last decade (Table 1). Three of the four RCTs have examined subglottic suctioning in a medical/surgical ICU population requiring ≥3 days of mechanical ventilation (1, 2, 4), the fourth RCT was limited to postcardiac surgery patients (3). Two trials report a statistically significant reduction in pneumonia in the test group (1, 4), the other two failed to show a difference (2, 3). A meta-analysis of the four RCTs shows a relative risk reduction of 0.49 (95% confidence interval, 0.39–0.71) in pneumonia. There was no effect on mortality, length of treatment in ICU, or duration of mechanical ventilation. One study using a decision-model analysis suggests that subglottic suctioning may be cost effective, despite the expense of the special tube and the administration of subglottic suctioning (3), but it is in line with a recent French RCT by Girou et al. (9) that reported 40% of patients who received subglottic suctioning developed laryngeal edema requiring reintubation. This complication of the normal endotracheal tube has a prevalence of <10% immediately after extubation (10).

Primary endogenous pneumonias are the main infectious problem in the ICU, as the prevalence is about 55% (Table 2). Primary endogenous pneumonia due to potential pathogens, both normal and abnormal, in general occurs within the first week of admission to the ICU (11). Previously healthy individuals, including trauma and surgical patients, develop early endogenous pneumonias with the normal potential pathogens such as *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*. Patients with underlying chronic conditions such as diabetes, alcoholism, and chronic obstructive pulmonary disease and who are referred to the ICU from home or from other wards and hospitals may carry abnormal aerobic Gram-negative bacilli such as *Klebsiella*, *Acinetobacter*, and *Pseudomonas* species.

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*See also p. 2071.

Key Words: mechanical ventilation; subglottic suctioning; laryngeal edema

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in their admission flora. This type of patient may develop a primary endogenous pneumonia with abnormal flora. Fortunately, most patients recover from their primary endogenous pneumonia after intensive care treatment including antibiotic therapy. About one third of ICU admissions may develop a late pneumonia, in general, after 1 wk of treatment in the ICU. These patients invariably acquire in their oropharynx abnormal aerobic Gram-negative bacilli that are associated with the ICU environment. This leads to secondary carriage and oropharyngeal overgrowth, migration, and colonization/infection of the lower airways. This sequence of events is termed secondary endogenous because the pneumonia is preceded by oropharyngeal carriage. Finally, *P. aeruginosa* has been described as possessing an intrinsic tropism to colonize lower airways rather than the oropharynx when both sites are equally accessible to bacterial entry (12). The pathogenesis of this type of pneumonia is termed exogenous because the lung is infected by *P. aeruginosa* after direct inoculation without previous carriage. The prevalence of exogenous lower airway infections is about 15%, and this exogenous pneumonia can occur at any time during treatment in the ICU.

Exogenous pneumonias are an inherent limitation of subglottic suctioning. Surveillance cultures of the oropharynx were not obtained in any of the four RCTs. If the subglottic secretions were to reflect oropharyngeal flora, two RCTs (1, 2) report exogenous pneumonias due to *P. aeruginosa* and Acinetobacter. In the RCT by Girou et al. (9), eight patients were randomized to receive subglottic suctioning vs. standard care in ten patients. Oropharyngeal and tracheal secretions were sampled daily and quantitatively cultured over a period of 2 wks. Practically all patients had tracheal aspirates positive for both normal and abnormal flora after day 1 of ventilation (75% in the test group vs. 80% in the control group). There was no significant difference in the daily bacterial counts of the oropharyngeal flora and in the trachea (5.1 log$^{10}$ colony-forming units/mL vs. 6.6 log$^{10}$ colony-forming units/mL in the control) between the two groups of patients. Apparently, suctioning of subglottic secretions does not prevent potential pathogens acquired in the oropharynx from migrating between the cuff of the endotracheal tube and the lower airway mucosa to colonize or infect the lower airway. Only one RCT allows the identification of the secondary endogenous problem, as 10 of the 15 pneumonias in the patients receiving subglottic suctioning were of secondary endogenous pathogenesis (2, 11). Thus, the preventative method of suctioning also fails to control the second type of late secondary endogenous pneumonia that, theoretically, suctioning might have controlled. Subglottic suctioning does not even affect primary endogenous pneumonias based on the human data by Girou et al. (9), which are in line with the microbiological data found by Dr. Berra and colleagues (8) in their sheep model. The lower airways of all animals were colonized/infected when the animals were ventilated with the special tube in a position similar to patients.

The conclusion is that none of the three types of pneumonias is controlled by subglottic suctioning. How can the reduction in pneumonia in two RCTs and the meta-analysis be explained? The difference is due to a reduction in pneumonias caused by the normal potential pathogens *S. pneumoniae*, *S. aureus*, and *H. influenzae*. This is highly likely to be an antibiotic rather than suctioning effect, in that a higher proportion of test patients are likely to have received adequate antimicrobials. This imbalance may be due to the enrolment into the test group of a higher number of trauma and surgical patients receiving commonly used antibiotics that cover the three normal bacteria (13). Interestingly, a 3-day course of parenteral ceftriaxone was compared with subglottic suctioning in an RCT including 57 medical/surgical patients (14). The protective effect of antimicrobials was significantly higher in preventing primary endogenous pneumonias than suctioning. *L’histoire se répète* in that the transient mortality reduction in patients randomized to bronchoscopy for diagnosing pneumonia compared with the noninvasive approach of tracheal aspiration was due to the immediate administration of adequate broad spectrum antibiotics in a French RCT including 413 patients (15).

### Table 1. Subglottic suctioning

<table>
<thead>
<tr>
<th>Author (Reference No.)</th>
<th>Type of Suctioning</th>
<th>Type of Patient</th>
<th>Sample Size</th>
<th>Pneumonia RR (95% Confidence Interval)</th>
<th>Mortality RR (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahul et al. (1)</td>
<td>Intermittent</td>
<td>Mixed</td>
<td>145</td>
<td>0.46 (0.23 to 0.93)</td>
<td>1.14 (0.62 to 2.07)</td>
</tr>
<tr>
<td>Valles et al. (2)</td>
<td>Continuous</td>
<td>Mixed</td>
<td>190</td>
<td>0.56 (0.31 to 1.01)</td>
<td>1.07 (0.70 to 1.65)</td>
</tr>
<tr>
<td>Kollef et al. (3)</td>
<td>Continuous</td>
<td>Cardiac</td>
<td>343</td>
<td>0.61 (0.27 to 1.40)</td>
<td>0.86 (0.30 to 2.42)</td>
</tr>
<tr>
<td>Smulders et al. (4)</td>
<td>Intermittent</td>
<td>Mixed</td>
<td>150</td>
<td>0.25 (0.07 to 0.85)</td>
<td>1.2 (0.55 to 2.61)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>828</td>
<td>0.49 (0.39 to 0.71)</td>
<td>1.1 (0.84 to 1.46)</td>
</tr>
</tbody>
</table>

RR, relative risk; mixed, medical/surgical.

### Table 2. Three different types of pneumonia due to “normal” and “abnormal” potentially pathogenic microorganisms (PPM)

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>PPM</th>
<th>Carriage</th>
<th>Time Cutoff</th>
<th>Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endogenous</td>
<td>Normal/abnormal</td>
<td>Present in admission flora</td>
<td>&lt;1 wk</td>
<td>c. 55</td>
</tr>
<tr>
<td>Secondary endogenous</td>
<td>Abnormal</td>
<td>Not present in admission flora, but acquired and carried later</td>
<td>&gt;1 wk</td>
<td>c. 30</td>
</tr>
<tr>
<td>Exogenous</td>
<td>Abnormal</td>
<td>No carriage at all</td>
<td>Anytime throughout the treatment in intensive care</td>
<td>c. 15</td>
</tr>
</tbody>
</table>

PPM, potentially pathogenic microorganisms; RR, relative risk.
Dr. Berra and colleagues (8) have made a major contribution to patient care in exposing an ineffective, costly method as unsafe. We predict that more methods without a positive impact, but expensive and not free from risk, including bronchoscopy to diagnose pneumonia, will travel along the same path. The end of suctioning is nigh, and that is good news for the critically ill.

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Noninvasive interfaces: Should we go to helmets?*

Noninvasive administration of positive pressure, in the form of either noninvasive ventilation (NIV) using the combination of pressure support and positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP), has been shown to improve the outcomes of patients with certain forms of acute respiratory failure compared with conventional therapy. For example, randomized trials have demonstrated that NIV using pressure support significantly reduces the need for intubation as well as hospital morbidity and mortality rates and length of stay in patients with acute respiratory failure due to chronic obstructive pulmonary disease exacerbations (1, 2). Similar findings apply to immunocompromised patients with acute respiratory failure (3, 4), and both CPAP alone (5) and NIV (6) rapidly improve respiratory distress and gas exchange while reducing the need for intubation in patients with acute pulmonary edema.

Despite these successes, however, noninvasive positive pressure still runs a substantial failure rate, ranging up to 40% in some studies (7). At least part of this failure rate is attributable to intolerance of the masks or “interfaces” that connect the pressure-generating devices to the patient’s upper airway.

Currently, the most commonly used interfaces to deliver noninvasive positive pressure to patients with acute respiratory failure are nasal and oronasal (or full face) masks. Recent evidence indicates that the oronasal mask has a higher initial tolerance rate than the nasal mask, and it has become the preferred initial mask in the acute setting (8). However, the need for this mask to seal over the nose and mouth contributes to mask intolerance because of facial discomfort and occasional ulceration. Therefore, interfaces that are capable of effectively providing noninvasive positive pressure

*See also p. 2090.

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without the need to seal around the nose and mouth have the potential of enhancing tolerance rates and thereby increasing the success rates of noninvasive positive pressure.

The “helmet” described in the current issue of Critical Care Medicine by Dr. Taccone and colleagues (9) represents one such approach to interface design. Resembling the diving helmets of yore, the helmet consists of a clear plastic cylinder that seals over the upper thorax and shoulders and is held firmly in place by straps under the axillae. Several studies have already reported the successful application of noninvasive positive pressure using the helmet to treat patients with a variety of forms of acute respiratory failure (10–11). However, one of these studies also raised concerns about CO2 rebreathing with the helmet because of a higher PaCO2 compared with controls associated with an increased inspired Pco2 (11).

Using a lung model and normal subjects, Dr. Taccone and colleagues (9) demonstrated that helmet use is associated with substantial CO2 rebreathing if CPAP is administered via a standard ventilator or at low flush rates with fresh gas. In their mathematical analysis, the authors attempted to demonstrate that the CO2 rebreathing behaves as although it is occurring in a “semiclosed environment,” like a room with a ventilation system. The mathematical formula was derived from that for CO2 homeostasis; the partial pressure of CO2 is equal to the square root of PaC02. Thus, the results are what would be anticipated intuitively; the higher the flushing rate in the helmet, the lower the level of CO2. However, the authors have not proven their hypothesis that the helmet functions as a “semiclosed environment” in which CO2 rebreathing is independent of mask volume and is “fundamentally different” from traditional interfaces. They tested only two helmet volumes and not a range, and they did not test other interfaces. It seems conceivable that other interfaces would not behave similarly with respect to the mathematical model; increased flushing rates should reduce rebreathing regardless of the interface. With standard masks, interface volume would be anticipated to affect rebreathing if it increases deadspace significantly, but even then, rebreathing should be minimized by high flushing rates, as suggested by Fergusonson and Gilmartin (12). These authors showed that during “bilevel” noninvasive ventilation administered via a standard nasal mask, sufficient expiratory pressure (corresponding to expiratory flow rate) essentially eliminated rebreathing.

Regardless of whether we accept the authors’ hypotheses, however, several important points derive from the Taccone study. The study highlights the need to thoroughly evaluate new interfaces that represent substantial departures in design before they are endorsed for widespread use. The study also clearly demonstrates that the helmet should not be used to administer CPAP from a standard ventilator or at low flush rates because certain patients, particularly those with high CO2 production rates, can retain substantial amounts of CO2. The authors’ recommendations that the helmet be used only with high-flow CPAP systems and that Pco2 be monitored in some way during helmet use are sensible, although they have not determined how the latter should be done. Pending more definitive studies, it seems advisable to check occasional arterial blood gases during helmet use to ascertain PaCO2 levels.

In addition, although Dr. Taccone and colleagues (8) did not assess use of the helmet to deliver pressure support and PEEP from a standard ventilator, their study raises major concerns about the occurrence of rebreathing during delivery of this form of NIV. Such an approach would also raise the concern of how to compensate for the compliance of the helmet (which is undoubtedly greater than that of traditional interfaces) that could blunt the rate of pressure delivery and interfere with patient-ventilator synchrony.

Interfaces like the helmet that avoid sealing around the nose and mouth are welcome additions to our interface armamentarium because they offer options to patients who are intolerant of traditional interfaces and have the potential of improving overall CPAP and NIV success rates. Eventually, these devices are likely to assume important roles in the noninvasive management of such patients with acute respiratory failure. However, studies like that of Dr. Taccone and colleagues (8) sound a cautionary note. Each new interface approach should underg a careful evaluation so that effects on rebreathing and ventilator performance can be fully understood before widespread application.

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Hypothermia during cardiac arrest: Moving from defense to offense*

More than 350,000 Americans die as a result of sudden cardiac arrest every year (approximately 1,000 people every day) (1). About 10–30% of long-term survivors have permanent brain damage as a result of global brain ischemia (2). Recently, hypothermia has been shown to make a difference. In 2002, two randomized, controlled, clinical trials demonstrated significantly improved outcomes in patients treated with hypothermia (surface cooling) after cardiac arrest (3, 4). Patients were cooled to 32–34°C for 12 to 24 hrs. Last year the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (ILCOR) recommended cooling for unconscious patients after out-of-hospital cardiac arrest from ventricular fibrillation (5).

Cooling can be started before arrest (protection), during arrest (preservation), and after arrest (resuscitation). The degree of hypothermia can be mild (34–36°C), moderate (27–32°C), or deep (10–20°C). Induction of hypothermia before cardiac arrest has been used successfully since the 1950s to protect the brain against global ischemia during cardiac surgery (6, 7). With prearrest induction of hypothermia, the lower the temperature, the better the protection. Therapeutic hypothermia after cardiac arrest in humans was explored in the late 1950s but was essentially abandoned because of uncertain benefit, slow cooling techniques, and side effects such as shivering, arrhythmias, and infection. With postarrest induction of hypothermia, there is a complex relationship between timing, depth, and duration such that early onset of treatment may be combined with milder hypothermia and shorter duration, whereas later onset seems to require deeper hypothermia and a longer duration to show a benefit. Since the 1980s, induction of hypothermia after return of spontaneous circulation (resuscitative hypothermia), in various animal models using various strategies, has been associated with improved functional recovery and reduced cerebral histologic deficits.

In this issue of Critical Care Medicine, Dr. Nozari and colleagues (8) report the results of a study of preservative hypothermia (starting hypothermia during resuscitation) delivered with venovenous extracorporeal cooling. Twenty-seven dogs were subjected to cardiac arrest and randomly assigned to one of four groups: 1) normothermic controls, 2) moderate hypothermia (27°C) started during resuscitation using venovenous extracorporeal cooling, 3) mild hypothermia (34°C) started during resuscitation using venovenous extracorporeal cooling, and 4) normothermic controls but with venovenous extracorporeal shunting. Thus, there were 12 normothermic dogs (groups 1 and 4) and 12 hypothermic dogs (groups 2 and 3); three dogs were excluded. The primary end points were functional outcome (overall performance score), neurologic function (neurologic deficit score), and histologic outcome (histologic damage score). The results showed that all 12 normothermic dogs died except one who survived but remained comatose. In contrast, all 12 hypothermic dogs not only survived but also had normal or near normal function and brain histology. This is impressive.

This study is important for several reasons beyond the impressive outcomes. First, although the powerful protective effect of intra-ischemic hypothermia has been known for decades, technical issues and practicality limited this approach in the clinical setting of cardiac arrest. There was also an underlying fear that cooling patients during resuscitation would somehow hamper and delay return of spontaneous circulation. In the current study, the authors have shown that it is feasible to induce hypothermia during cardiac arrest, in which it can potentially have a greater effect and may be combined with a brief duration. There may be additional long-term benefits as well. Dietrich et al. (9) have demonstrated that intra-ischemic hypothermia may be more likely to result in permanent reduction of neuronal damage rather than simply delaying neuronal death. Second and almost equally important, the authors have reported that mild hypothermia (34°C) was just as good as deeper levels of hypothermia (27°C). This has been reported before (10), but it is worth confirming if only because it seems counterintuitive. Although moderate hypothermia is also generally safe, targeting temperatures of 34°C is easier. Finally, venovenous extracorporeal cooling, as in this study, cooled extremely rapidly. The time to reach the target temperature of 34°C was remarkably only a few minutes. In contrast, surface cooling is slow and cumbersome and takes several hours. New endovascular, counter-current, heat-exchange catheters seem to be faster (11). Venovenous extracorporeal cooling, however, seems to be faster still, albeit less practical. Further studies are needed to determine the quickest, safest, and best way to cool patients with cardiac arrest.

The late Dr. Peter Safar is credited for the very idea of cerebral resuscitation at the same time as cardiopulmonary resuscitation (cardiopulmonary–cerebral resuscitation). In 1961, Dr. Safar assembled nine steps of cardiopulmonary–cerebral resuscitation beginning with the now familiar ABCs of resuscitation, airway, breathing, and circulation (12). Resuscitative hypothermia, however, was listed as step H, after stabilization. This study represents another step toward Dr. Safar’s vision of cooling patients early during resuscitation, in a sense moving from a defensive approach (trying to attenuate damage that has already occurred) to an offensive approach (trying to prevent the damage in the first place). Cardiac arrest

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can be devastating for patients and families and frustrating for intensivists who provide care. Innovative clinical approaches, such as ultra-early preservative hypothermia and cerebral blood flow promotion, are needed to make a breakthrough.

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